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Patent controversies and court cases
Cancer diagnosis, therapy and prevention

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Patents are issued essentially by all countries on inventions that are deemed novel, non-obvious, clearly described and of significant utility or industrial application. The only exceptions to patenting an invention are abstract ideas, laws of nature and natural phenomena, although the exceptions vary depending on countries where moral, public order or human rights considerations are also taken into account. Although patent laws are updated over decades, the rapid progress of science creates situations that the patent laws on the book cannot address, leading to contentious legal issues. This is often true for life saving drugs, particularly drugs for cancers or HIV/AIDS, which are expensive and beyond the reach of poor people because of the proprietary positions of these patented drugs. Another contentious issue is the patent eligibility of human genes and mutations that are often thought of nature's contribution to human health and propagation and should be beyond the reach of patentability. In this review, we address some of these current legal issues and their implications for the development of diagnostic methods, therapeutic interventions and even prevention for cancer, a scourge of mankind.

Introduction

The July 2011 ruling by the United States Court of Appeals for the Federal Circuit (CAFC) upholding the validity of patents for isolated and purified human genomic DNA has reignited the controversy over patent eligibility of scientific inventions involving life forms including human genes. This CAFC decision, on appeal, has led to the March 2012 decision by the US Supreme Court ordering the CAFC to reconsider its decision based on the Supreme Court verdict on a case known as *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, no. 10-1150 (s. Ct. 2012). In this case, the US Supreme Court held that claims directed to optimization of drug dosages for drug efficacy studies are basically mental exercises and are therefore invalid under 35 USC section 101. The relevance of the Prometheus case with the underlying principles of the patenting of human genes and/or mutations is not obvious and raises an interesting question: does the US Supreme Court decision declaring "anything under the sun that is made by man" is patent eligible in the US (*Diamond v. Chakrabarty*, 447 US 303, 1980) still hold true? We say yes!

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US Constitution, Patent Laws and their Interpretation

The US patent laws are a part of the US Constitution framed in 1790 with subsequent amendments under Title 35, Section 101 (35 USC section 101) with the stated objective, "whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title." There are some statutory requirements for an invention to be patent eligible, viz., an invention must have novelty (35 USC section 102), must be non-obvious (section 103) and must be described in detail to enable a person skilled in the art to be able to reproduce the invention (section 112). However, as stated in section 101 and section 112 first paragraph, a patentable invention must be useful and the utility should be specific, substantial and credible.

There are two US Supreme Court decisions that have guided the patent eligibility issues, particularly for inventions related to life forms or products derived therefrom such as DNA, antibodies, cells, genes, etc. The US Supreme Court in *Diamond v. Chakrabarty*, 447 US 303 (1980) declared "anything under the sun that is made by man" is patent eligible so long as it meets the statutory requirements of 35 USC sections 101, 102, 103, 112, etc. A second Supreme Court decision *Diamond v. Diehr*, 450 US 175 (1981) provided guidelines to what are non-patentable inventions, namely, laws of nature, natural phenomena and abstract ideas and the resolution of many patent infringement cases has depended on such Supreme Court guidelines.[1,2] Since essentially all cancers are due to accumulated mutations in the human genome,[3,4] and a few such mutations can be inherited, leading to predisposition to some cancers, efforts have been made to diagnose such mutations in people with a family history of a particular cancer, as well as patenting of such screened mutations. Such patenting of diagnostic mutations, as well as the genes that are mutated, has led to major controversies on the legality of patenting human genes and mutations.

The Court Case on Human Gene Patents: *Association of Molecular Pathology v. USPTO*

In May 2009, the Association for Molecular Pathology, clinicians and patient groups, along with American Civil Liberties Union

(ACLU) and the Public Patent Foundation (PUBPAT) filed a lawsuit against the US Patent and Trademark Office (USPTO) at the Federal District Court in New York City to have Myriad Genetics patents on the *BRCA1* and *BRCA2* genes and their mutations, that predispose women to breast and ovarian cancers, revoked. In response, Judge Robert Sweet of the District Court at the Southern District of New York in March, 2010 revoked seven US patents issued to the University of Utah Research Foundation and Myriad Genetics. These patents covered the commercial and non-commercial use of *BRCA1* and *BRCA2* genes and their mutations and genetic rearrangements. Judge Sweet argued that such patented genes are simply products of nature as they occur in the human genome and are non-patentable. This decision was reversed by the Court of Appeals for the Federal Circuit (CAFC) in July 2011, upholding the patent eligibility of all the claims on isolated and purified human genes. The three-judge CAFC panel held c-DNA forms to be patent eligible while isolated and purified DNA forms led to a split with one member judge finding the scope of the structural changes in isolated DNA insufficient to allow its patentability. The question of the standing of the plaintiffs in bringing this lawsuit was also considered because of a single clinician expressing his actual and immediate intention to practice the invention if the patents were held invalid. The court, however, expressed strong negative feelings about the patent eligibility of the comparison of nucleotide sequences in various *BRCA* genes, arguing that these are mental exercises without any involvement of machines or transformative processes and are therefore non-patentable subject matters. On appeal, the Supreme Court, in a unanimous decision, referred the patentability of the BRCA patent claims back to the CAFC. The Supreme Court, in March 2012, sent the case to the CAFC to reconsider it based on the Prometheus decision, as mentioned earlier. The oral arguments on the case began at the end of July, 2012, and in mid-August, 2012 the same three-judge panel of the CAFC again upheld the DNA claims of the Myriad Genetics patents but held as patent-ineligible the diagnostic claims on the analyses of the BRCA1/2 mutations. Thus, a final outcome of this case may yet be decided by the US Supreme Court if an appeal is granted.

Why BRCA1/2 Gene Mutations and Rearrangements Deserve Patent Protection?

The CAFC panel rightly rejected the District Court ruling that isolated and purified human DNA are products of nature, pointing out that there is a long tradition of granting patents to purified natural products such as adrenaline [*Parke-Davis and Co. v. H.K. Mulford Co.*, 189 F.95, 103, S.D.N.Y. (1911)]. Although Myriad Genetics cited this case, Judge Sweet argued that this was not a question of patentability at that time but a question of novelty and subsequent Supreme Court decisions mandate distinctive characteristics of the patentable product as opposed to a purely natural product.

We have recently argued[5] that apart from non-obviousness, novelty (that required significant human intervention to locate and characterize the two *BRCA* genes in chromosomes 13 and 17) and detailed descriptions, enabling and allowing the USPTO to issue the contested patents, the screenings and genetic testing of the mutations in the *BRCA* genes, that predispose women to breast and ovarian cancers, are of great utility to the vulnerable women with family history of such cancers. Such utility, along with the other criteria mentioned above, satisfy the requirements of 35 USC sections 101, 102, 103 and 112 to allow patentability of BRCA1/2 gene mutations. It is important to note, however, that the USPTO should not have issued the patents on the *BRCA1* and *BRCA2* genes as they have no utility per se.[5] There are about 22,000 genes in the human genome and present day sequencing technology allows complete sequence of a human genome at a low cost. Thus it would be possible for a person to patent any and all isolated human genes in absence of a specific, substantial and credible utility of the genes, but hoping to find such utility in the future. This may happen in UK, however, because of the recent UK Supreme Court decision, lowering the bar of utility in granting patent protection, in the court case *Human Genome Sciences v. Eli Lilly* (UKSC 51, 2011). Without the mutations, having access to the *BRCA* genes does not impart any particular usefulness. Revoking the patents for *BRCA1* and *BRCA2* genes will allow many clinicians to look for other mutations and genetic rearrangements in the *BRCA* genes without infringement of the Myriad Genetics patents on their patented mutations/rearrangements.

There is Supreme Court Precedent for Allowing Patentability of Mental Exercises When Such Exercises are Tied to a Useful Invention

It may seem like a contradiction in our argument that while isolated and purified DNA involving a great deal of human intervention and ingenuity should be patent eligible, the specific genes present in such DNA should not be patentable unless such genes satisfy the statutory requirements of patentability including specific, substantial and credible utility. What makes Myriad's isolated and purified DNA harboring the *BRCA* genes patentable is the utility of any mutations present in the genes conferring predisposition to cancers, thereby transforming an unpatentable mental exercise to a patent-eligible application of such an exercise. This argument follows from the US Supreme Court decision in *Diamond v. Diehr*, 450 US 175 (1981). The Diehr application involved a process of using a mathematical equation to determine the optimum time of curing of synthetic rubbers, taking readings at fixed intervals of the amount of curing and using the mathematical equations to calculate the optimum curing process. Thus the mathematical equations are an important ingredient of the invention, even though they are a part of the mental process. The Supreme Court allowed the process patent for curing rubber using the equation, pointing out that even though the equations represent a non-patentable mental exercise, their useful application to determine the optimum curing process makes the process patent eligible. Thus even though the isolated DNA fragments with *BRCA1* and *BRCA2* genes are not patentable because of a lack of demonstrated utility, and the sequence comparisons among these genes to define the mutations that predispose women to breast and ovarian cancers are basically a mental

Table 1. Results of human phase I clinical trials of p28 in stage IV cancer patients with metastatic, refractory solid tumors

Patients		Type of cancer	Study design[a]	Treatment dosage (mg p28/Kg body weight) (in escalating doses)	Overall response[b]	Clinical trial identifier	Sponsor
n = 15	11 male 4 female	Melanoma (7) Colon (4)	i.v. bolus of p28 3 times per week for 4 weeks	0.83 1.6	Stable disease (6/15)	NCT00914914	CDG Therapeutics, Inc.
Age range	50–80	Sarcoma (2) Pancreatic (1)		2.5 3.33	Partial tumor regression (2/15, 1 prostate, 1 melanoma)		
Median	62	Prostate (1)		4.16	Complete regression (2/15, 1 sarcoma, 1 melanoma)		

[a]Observation two weeks before the next higher dose; [b]no immune response or adverse effect even at maximum dosage of p28. Data taken from a presentation made at the ASCO meeting in Chicago on June 6, 2011.[9]

exercise, the combination provides the utility required to satisfy section 101 of 35 USC to confer validity to the Myriad patents on BRCA1 and BRCA 2 gene mutations.

Moving Forward

The screening of BRCA1 and BRCA2 mutations in women with a family history of breast or ovarian cancers is very important for these women to take precautionary measures, including surgical removal of breasts and ovary, if the screening results are positive. For essentially all women, but particularly for young women of child bearing age, the positive tests are devastating, unless some measures can be taken to prevent the appearance of the cancers in the target organs. We have recently addressed this issue by demonstrating that a bacterial protein, and a peptide derived from it, have not only demonstrated anticancer activity including entry specificity in cancer cells but in laboratory experiments demonstrate cancer preventive activity as well.[6-8] Coupled with the fact that a chemically-synthesized peptide derived from such a protein (azurin), termed p28, demonstrated in phase I human clinical trials very little toxicity in 15 advanced stage (stage IV) cancer patients, allowing partial or sometimes complete regression of drug-resistant tumors in some patients (**Table 1**),[9] and also demonstrated cancer preventive activity in laboratory experiments (**Fig. 1**),[7,8] it would be of great interest to examine any cancer preventive effect of p28 in vulnerable women with BRCA1/BRCA2 mutations[6] or high-risk people with PALB2 mutations for pancreatic cancer or even other cancers such as glioblastoma multiforme.[10] If there is shown to be a statistically significant reduction of tumor emergence in such BRCA mutation-positive women taking p28 over a period of time, as opposed to those not taking it, it would further demonstrate the utility of BRCA1/BRCA2 gene mutation screening in the prevention of cancer emergence in vulnerable populations. Such utility may then be extended to many cancer patients where the cancers are in remission, but the patients are still worried about a relapse of their cancers. Protein/peptide drugs, similar to azurin/Laz/p28, can then be developed not only against drug-resistant cancers, but also against multiply-drug-resistant (MDR) bacteria such as MDR-*Pseudomonas aeruginosa*, methicillin-resistant *Staphylococcus aureus* or MDR-*Mycobacterium tuberculosis*.[11]

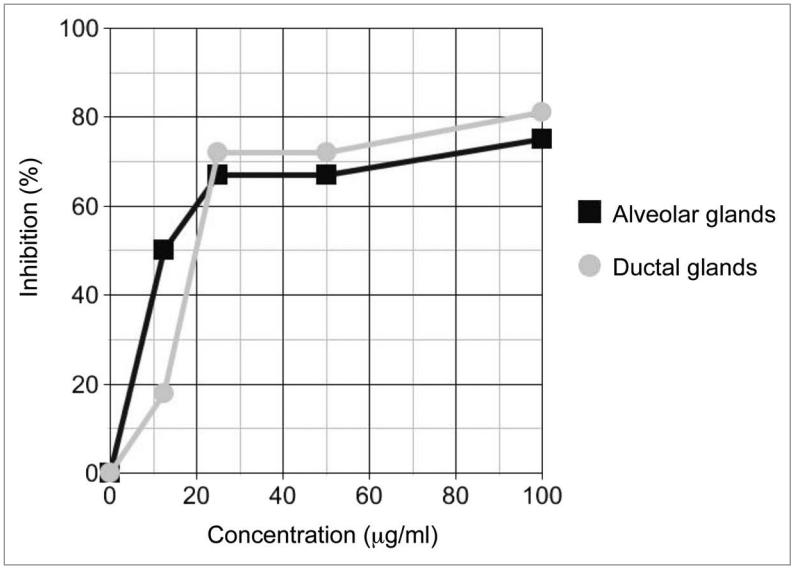

Figure 1. The inhibitory effect of p28 peptide on the development of precancerous lesions induced by 7,12-dimethylbenz[α]anthracene (DMBA) in alveolar and ductal glands (data taken from US patent 8,232,244).[7]

Beyond Patent Eligibility: Overriding Patents through Legal Means

The Myriad Genetics court case is an example of defining the limits of the patent eligibility of various inventions in the United States. However, the United States, and indeed many other countries have laws in the book that allow the government to ignore eligible and issued patent rights of an inventor and produce the

patented product through contractors or third parties without a license from or approval of the patent holder. Such a legal procedure is called compulsory licensure, which enables a government to ignore the patent rights involving a product or a process during or in the name of a national emergency or needs encompassing national security or medical emergency.[12] Such laws, allowing compulsory licensing, are in the books of the United States and many European countries such as France, Belgium or Switzerland. The US Government's legal authority under 28 USC 1498 allows the government to use a patented device such as camouflage screens for military use (as in *Brunswick Corp. v. US*, 152 F. 3d 946, 1998) or devices that allow space satellites to remain in orbit in proper orientation (*Hughes Aircraft Co. v. US*, 86 F. 3d 1566, Fed. Cir. 1996) with appropriate compensation, amounting to conventional royalty payment, to the patent holder. However, the enforcement of compulsory licensure in case of medical emergency has been fewer in the United States than in countries such as South Africa or Thailand where the rising costs of drugs, particularly against HIV/AIDS, have forced the governments to threaten or use compulsory licensure to reduce the costs of medicines in specific diseases. The TRIPS (Trade-Related Aspects of Intellectual Property Rights) agreement, signed in 1996 by 140 nations who are members of the World Trade Organization (WTO), mandates member countries to respect the patent laws of other member countries, although Article 31 of the TRIPS agreement does authorize individual member countries to use compulsory licensure in case of medical, public health or national emergencies.

In March 2012, the Indian Patent Office authorized a compulsory license under a provision of the Indian Patent Laws to allow an Indian company Natco Pharma to produce a patented anticancer drug Nexavar (chemical name Sorafenib, developed jointly by Bayer, Leverkusen, Germany and Onyx, Emeryville, USA). Sorafenib fights cancers by targeting vascular endothelial growth factor receptors (VEGFR) 2 and 3 as well as platelet derived growth factor receptor (PDGFR) β active against melanoma, renal cell carcinoma or hepatocellular carcinoma. This is the first example of using the compulsory licensure in India under an amended version of the Indian Patent Act that allows the Indian Patent Office to use this provision for life saving drugs that must be "reasonably affordably priced," citing the Bayer's cancer drug cost at around $5,000 a month as too costly and unaffordable. As mentioned earlier, similar legal provisions have also been used by Thailand and South Africa for cancer or HIV/AIDS drugs. It is interesting to note in this context that a Bayer antibiotic drug, Ciprofloxacin, known as Cipro, became a subject of discussion for the use of the provisions of 28 USC 1498 during the anthrax bioterrorism scare in the United States in 2001.[12] However, to the credit of the United States Government, the government used the compulsory licensure threat to negotiate with Bayer to reduce the price of Cipro by more than 70% so as to stockpile Cipro in case of a wider anthrax threat that of course never materialized.[12] Thus the compulsory licensure provisions in the patent laws of many countries, particularly developing countries, have kept the drug prices low for many life-saving drugs, including anticancer drugs.

Incremental Innovation and Anticancer Drugs: A Court Case in India

Since 1970–72, Indian patent laws allowed process patents but did not recognize product patents for drugs and pharmaceuticals. Under the TRIPS agreement, the Indian patent laws were amended in 2005 to permit the patenting of pharmaceutical products. The non-patentable subject matters in the Indian Patent Act include laws of nature, mathematical calculations, plants, animals, methods of agriculture or medical treatment as well as subject matters that are contrary to public morality. However, in order to prevent established pharmaceutical companies, particularly foreign multi-national corporations, to make incremental improvements to their existing drugs and other products/processes to extend patent protection, Indian patent laws had a clause, section 3(d), that discouraged incremental innovations in the form of new uses such as new routes of administration, new dosages or new forms of an existing drug for patent protection, which are normally allowed in most other countries including the United States. The section 3(d) was purportedly introduced to prevent patent thickets or patent ever-greening (a collection of related patents) which could lead to higher prices of drugs by extending the life span of the patent(s) and delaying the generic makers to bring cheap versions to the market place. Of course, even with patent protection of the incrementally improved drug, the original drug, whose patent might have expired, could be produced cheaply by the generics makers. Among non-patentable subject matters under section 3(d) is the mere discovery of any new property, new use or new form of a known substance which does not result in the significant enhancement of efficacy, such as salts, esters, ethers, polymorphs, metabolites, isomers or their mixtures. As the amended patent laws took effect in 2005, the Assistant Controller of Patents rejected an application from Novartis filed in 1998 for patenting the crystalline form of the drug Gleevec (Imatinib mesylate) that targeted a fusion protein Bcr-Abl formed due to the chromosomal translocations in patients with chronic myeloid leukemia (CML).[13] To counter the patent office decision, Novartis argued that the polymorphic salt form of imatinib increased bioavailability of this drug by 30% than the patented free base form of imatinib and therefore merited a patent. The basic imatinib patent is valid in the US until 2015. However, the basic patent was never filed in India and this secondary patent application on the modified form of imatinib is the only protection Novartis will have in India. Using section 3(d), the Assistant Controller of Patents rejected Novartis's appeal arguing that such increase alone did not constitute significant enhancement of efficacy, whereupon in 2006, Novartis appealed to the Madras High Court to reject section 3(d) as being vague and arbitrary, as well as unconstitutional and contrary to TRIPS provisions. The Madras High Court ruling did not address the TRIPS provision as it had no jurisdiction over the issue, leaving the dispute resolution to the WTO Dispute Settlement Body. The High Court, however, rejected Novartis's arguments of 30% enhancement of bioavailability as a patentable and significant enhancement of the therapeutic efficacy of the drug. The question of lack of significant therapeutic efficacy under section

3(d) also prompted the Delhi High Court in 2009 to reject a request of an injunction from Hoffman La-Roche against Cipla from marketing a generic version of Roche's anticancer drug Tarcerva, arguing that Roche failed to demonstrate significant therapeutic efficacy in support of its original patent application. The Novartis appeal is presently being considered by the Indian Supreme Court and a decision will likely emerge soon. Such a decision, similar to the 1980 *Diamond v. Chakrabarty* decision by the US Supreme Court on the patent eligibility of genetically-engineered life forms in the United States, will dictate what kind of incremental innovation, if any, is patent eligible in India and how will such decisions be reached by the Indian Patent Office with limited human and financial resources. There are also impending questions about stricter interpretation of section 3(d) to reject older primary patents issued before 1995, as the Gleevec patent was in the US, and how secondary patents will affect the marketing and availability of other anticancer drugs produced by the multinational pharmaceutical companies.

Concluding Remarks

Cancer is widespread in all countries and anticancer drugs are in great demand with annual sales of $120 billion just in the United States. Consequently, development and patenting of anticancer drugs, including incremental improvements in the bioavailability or efficacy of such drugs, are of great value to the patients as well as to the drug producers. Similarly, early diagnosis of cancers, as well as screenings and evaluations of genetic predispositions, can be life-saving for many potential cancer patients. In this sense, detection of genetic mutations such as BRCA1 or BRCA2 could be of great value if preventive measures can be taken for the cancers before they emerge. In this context, the emergence of potential cancer therapeutics, as well as cancer preventive, drugs such as p28[7,8] might be of practical value to the people with predisposition to cancer. p28 has not only cancer preventive property, but in phase I human clinical trials in 15 stage IV cancer patients (**Table 1**), it was shown to be non-toxic even at the highest dose where it demonstrated significant cancer regressing effects, including partial and complete regressions in some cases, in such patients with drug-resistant cancers.[9] The effect of p28 on cancer stem cells has not yet been studied and its mode of cancer preventive action is unknown. The next step would be to demonstrate the cancer preventive ability of p28 in mouse models where tumors such as glioblastomas[14] or lung cancers[15,16] can be triggered in mice with viral vectors harboring activated oncogene mutations such as H-RAS, AKT, TP53 or K-RAS. Intraperitoneal or other forms of injections or nasal inhalations of p28 in such mice before, during or after the viral-mediated activated oncogene delivery to the mice and following the numbers and sizes of the tumors will provide important information on the potential utility of emerging drugs such as p28 in preventing cancer development in vulnerable people, including women harboring BRCA1/2 mutations, to clearly demonstrate the utility of the development of diagnostic methods for screening disease-causing genetic mutations. It should be emphasized here that p28 is a part of azurin with limited cancer-killing domains. There are other domains in azurin with anticancer property[17] that should provide better efficacy and will likely make azurin less susceptible to resistance development,[6,11] provided lack of toxicity of azurin in animals and cancer patients can be demonstrated, as has been done for p28. It is also interesting to note that such domains of azurin that target hyper-expressed surface receptors similar to EphB2[17] in cancer cells such as lung cancers can be used in enhanced radiation therapy with conjugated radiosensitizers such as nicotinamide,[18] providing an additional armor in our fight against cancers. It should be emphasized here that azurin, when injected in the peritoneum of mice harboring human tumors such as melanoma or breast cancer at 1.0 mg dose three times a week, demonstrated inhibition of cancer growth by 58 to 85%, but no apparent toxicity in such mice,[19,20] indicating that azurin may resemble p28 as being non-toxic in humans as well. Additionally, an interesting question is: how does azurin or p28 inhibit DMBA-induced pre-cancerous lesion formations in mouse mammary cells? Since azurin (or p28) is known to enter preferentially to cancer cells and form complexes with intracellular proteins known to be involved in cancer growth such as p53, VEGFR, etc.,[19-22] can immuno-precipitation with anti-azurin antibodies in DMBA-treated and non-treated mouse mammary cells indicate which proteins might be involved in carcinogen-induced triggering of cancers, perhaps giving us some clue on how some environmental carcinogens trigger the initiation of the oncogenic process in our cells?

Patent laws, because of the rapid advancement of science in unknown territories, are often murky, out-dated, lack clarity and are difficult to interpret, leaving such interpretations to the judiciary, including the Supreme Courts of various countries. Some of the members of the judiciary may have little science background and decisions on complex scientific advances are often made on the evolving laws of the land, demonstrating a need for a reference international court and science education to judges.[23] This is particularly true in life sciences involving human genes, their patentability, costs associated with patented drugs and diagnostic procedures and the underlying emotional issues on genetic inheritance, cancers, life and death.

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References

1. Chakrabarty AM. Bioengineered bugs, drugs and contentious issues in patenting. Bioeng Bugs 2010; 1:2-8; PMID:21327122; http://dx.doi.org/10.4161/bbug.1.1.9850.
2. Fialho AM, Chakrabarty AM. The role and importance of intellectual property generation and protection in drug development. In Fialho AM, Chakrabarty AM, eds. Emerging Cancer Therapy: Microbial Approaches and Biotechnological Tools, Nutley: John Wiley & Sons, 2010: 405-19.
3. Cancer Genome Atlas Research Network. Integrated genomic analyses of ovarian carcinoma. Nature 2011; 474:609-15; PMID:21720365; http://dx.doi.org/10.1038/nature10166.
4. Cancer Genome Atlas Network. Comprehensive molecular characterization of human colon and rectal cancer. Nature 2012; 487:330-7; PMID:22810696; http://dx.doi.org/10.1038/nature11252.
5. Fialho AM, Chakrabarty AM. Law-medicine interfacing: patenting of human genes and mutations. Recent Pat DNA Gene Seq 2011; 5:81-5; PMID:21574951; http://dx.doi.org/10.2174/187221511796392015.
6. Chakrabarty AM. Bacterial proteins: A new class of cancer therapeutics. J. Commercial Biotechnol 2012; 18:4-10.
7. Das Gupta TK, Chakrabarty AM, Beattie C, Yamada T. Compositions and methods to prevent cancer with cupredoxins. US Patent 8,232,244 issued on July 31, 2012.
8. Mehta RR, Hawthorne M, Peng X, Shilkaitis A, Mehta RG, Beattie CW, et al. A 28-amino-acid peptide fragment of the cupredoxin azurin prevents carcinogen-induced mouse mammary lesions. Cancer Prev Res (Phila) 2010; 3:1351-60; PMID:20841487; http://dx.doi.org/10.1158/1940-6207.CAPR-10-0024.
9. Richards JM, Warso MA, Mehta D, Christov K, Schaeffer CM, Yamada T, et al. A first-in-class, first-in-human phase I trial of p28, a non-HDM2-mediated peptide inhibitor of p53 ubiquitination in patients with metastatic refractory solid tumors. J Clin Oncol 2011; 29: Abstract 2511 (ASCO Annual Meeting).
10. Fialho AM, Salunkhe P, Manna S, Mahali S, Chakrabarty AM. Glioblastoma multiforme: novel therapeutic approaches. ISRN Neurol 2012; 2012:642345; PMID:22462021.
11. Avner B, Fialho AM, Chakrabarty AM. Overcoming drug resistance in multi-drug resistant cancers and microorganisms: a conceptual framework. Bioeng Bugs 2012; 3:262-7-8; PMID:22179143.
12. Resnik DB, DeVille KA. Bioterrorism and patent rights: "compulsory licensure" and the case of Cipro. Am J Bioeth 2002; 2:29-39; PMID:12230852; http://dx.doi.org/10.1162/152651602760250084.
13. Druker BJ, Lydon NB. Lessons learned from the development of an abl tyrosine kinase inhibitor for chronic myelogenous leukemia. J Clin Invest 2000; 105:3-7; PMID:10619854; http://dx.doi.org/10.1172/JCI9083.
14. Marumoto T, Tashiro A, Friedmann-Morvinski D, Scadeng M, Soda Y, Gage FH, et al. Development of a novel mouse glioma model using lentiviral vectors. Nat Med 2009; 15:110-6; PMID:19122659; http://dx.doi.org/10.1038/nm.1863.
15. Meylan E, Dooley AL, Feldser DM, Shen L, Turk E, Ouyang C, et al. Requirement for NF-kappaB signalling in a mouse model of lung adenocarcinoma. Nature 2009; 462:104-7; PMID:19847165; http://dx.doi.org/10.1038/nature08462.
16. Hollander MC, Maier CR, Hobbs EA, Ashmore AR, Linnoila RI, Dennis PA. Akt1 deletion prevents lung tumorigenesis by mutant K-ras. Oncogene 2011; 30:1812-21; PMID:21242979; http://dx.doi.org/10.1038/onc.2010.556.
17. Chaudhari A, Mahfouz M, Fialho AM, Yamada T, Granja AT, Zhu Y, et al. Cupredoxin-cancer interrelationship: azurin binding with EphB2, interference in EphB2 tyrosine phosphorylation, and inhibition of cancer growth. Biochemistry 2007; 46:1799-810; PMID:17249693; http://dx.doi.org/10.1021/bi061661x.
18. Micewicz ED, Jung C-L, Schaue D, Luong H, McBride WH, Ruchala P. Small azurin derived peptide targets ephrin receptors for radiotherapy. Int J Pept Res Ther 2011; 17:247-57; http://dx.doi.org/10.1007/s10989-011-9265-9.
19. Yamada T, Goto M, Punj V, Zaborina O, Chen ML, Kimbara K, et al. Bacterial redox protein azurin, tumor suppressor protein p53, and regression of cancer. Proc Natl Acad Sci U S A 2002; 99:14098-103; PMID:12393814; http://dx.doi.org/10.1073/pnas.222539699.
20. Punj V, Bhattacharyya S, Saint-Dic D, Vasu C, Cunningham EA, Graves J, et al. Bacterial cupredoxin azurin as an inducer of apoptosis and regression in human breast cancer. Oncogene 2004; 23:2367-78; PMID:14981543; http://dx.doi.org/10.1038/sj.onc.1207376.
21. Domenici F, Frasconi M, Mazzei F, D'Orazi G, Bizzarri AR, Cannistraro S. Azurin modulates the association of Mdm2 with p53: SPR evidence from interaction of the full-length proteins. J Mol Recognit 2011; 24:707-14; PMID:21584881; http://dx.doi.org/10.1002/jmr.1105.
22. Mehta RR, Yamada T, Taylor BN, Christov K, King ML, Majumdar D, et al. A cell penetrating peptide derived from azurin inhibits angiogenesis and tumor growth by inhibiting phosphorylation of VEGFR-2, FAK and Akt. Angiogenesis 2011; 14:355-69; PMID:21667138; http://dx.doi.org/10.1007/s10456-011-9220-6.
23. Zweig FM. The limiting factor. Biotechnology and the charter for an international science and technology reference court. Not Polit 2002; 18:51-8; PMID:15505917.